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Korfel, Agnieszka ; Chamberlain, Marc ; Neuwelt, Ed ; Thiel, Eckhard ; Doolittle, Nancy ; Schlegel, Uwe ; Dreyling, Martin ; Rubenstein, James ; Fischer, Lars ; Björkholm, Magnus ; Martus, Peter ; Weller, Michael ; Glantz, Michael

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# Therapy for Secondary CNS Involvement in Malignant Lymphomas: No Standard Yet!

**TO THE EDITOR:** The prognosis of secondary CNS involvement in systemic lymphomas (secondary CNS lymphoma, SCNSL) is poor, and the optimal treatment remains to be established. Because of the rarity of SCNSL and the lack of prospective trials, the level of evidence guiding therapy is low. Limited data suggest that intensive systemic chemotherapy, followed by high-dose chemotherapy and autologous stem-cell transplant (HD-ASCT), is the only potentially curative approach.

In their recent article in *Journal of Clinical Oncology*, Ferreri et al[1] report on a phase II trial of 38 patients with SCNSL treated with an antimetabolite-based chemotherapy followed by HD-ASCT. For all patients, the 2-year event-free survival (EFS; primary end point) was 50% and the 5-year EFS was 40%. The 5-year overall survival (OS) was 41% for all patients and 68% for those who completed HD-ASCT. The authors conclude that this regimen should be considered as the new standard of care for patients with SCNSL. This is a well-conducted and concisely reported trial, but there are several aspects that warrant commentary.

First, the complete omission of anthracyclines and vinca alkaloids, uniformly accepted as standard therapy of aggressive B-cell lymphomas, likely led to the undertreatment of chemotherapy-naïve patients, for whom rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone–like protocols, enriched by CNS-penetrating drugs such as high-dose methotrexate, may be a preferable treatment option, as currently practiced by others.

Secondly, study patients were heterogeneous with respect to histology (diffuse large B-cell [n = 32], mantle-cell [n = 3], and follicular [n = 3] lymphoma). The authors' assumption that histology does not affect outcome in SCNSL has never been substantiated. Moreover, both therapy-naïve patients with CNS involvement at diagnosis (n = 16) and pretreated patients with SCNSL at relapse (n = 22) were included, and there was a wide range between the time of lymphoma diagnosis and CNS involvement (0 to 69 months). Ferreri et al[1] contend that the outcome of SCNSL is similar, regardless of histology and pretreatment. However, because of the small sample size, these assumptions cannot be corroborated. For example, the difference in 5-year OS between patients with delayed SCNSL (5-year OS, 45%) and those with SCNSL at diagnosis (5-year OS, 36%) suggests a better prognosis for the delayed group (relative risk, 1.21); however, the precision of this estimate is low (95% CI, 0.56 to 2.65). Also, because 58% of patients (all with delayed SCNSL) received a wide variety of previous treatments further heterogeneity and potential bias were introduced.

Most importantly, despite the valuable information this trial provides, it is uncontrolled, and the primary outcome measure (2-year EFS) was assessed by unblinded treating investigators. Both of these features demand the assignment of class IV evidence for this study, which can never be the basis of standard-of-care decisions. Even ignoring this important issue, the trial failed to achieve its predefined primary outcome (a 2-year EFS of 60%). To demonstrate a convincing treatment effect using the same primary outcome measure, the same study parameters (significance of 0.05, power of 80%, uninteresting response rate of 40%) and the actual 2-year EFS seen in this trial (50%), 154 patients would have been required using the Fleming design used by the authors.

The third point concerns the feasibility of the proposed therapy. Ferreri et al[1] state that the protocol was tolerable, notwithstanding the reported dropout rate of 47% (18 of 38 patients). Moreover, it is stated that 123 (81%) of the 152 planned cycles were administered. However, in that HD-ASCT was included as planned therapy, it seems that only 65% (123 of 190) of planned cycles were administered.

The fourth point of concern pertains to the toxicity of the treatment. The toxicity-related death rate of 11% (95% CI, 4.2% to 24.1%) is formidable. In addition, three patients had grade 3 or 4 bleeding, two had *Aspergillus* pneumonia, one patient each had Guillain-Barré syndrome and a secondary malignancy, and an unspecified number of patients manifested cytomegalovirus reactivation. Ferreri et al[1] state that no late neurotoxicity was observed; however, the method and timing of evaluation are not stated.

The study by Korfel et al[2] illustrates that a relatively homogenous group of patients with SCNSL can be recruited and treated in a prospective multicenter study (all patients had aggressive lymphoma with SCNSL at relapse and were pretreated—the majority with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone); it also demonstrates that a chemotherapy-only regimen is feasible in patients with SCNSL and is associated with a relatively low dropout rate (80% completed the study protocol), and that a 2-year EFS of 50% can be achieved with an acceptable therapy-related death rate of 3%.

The protocol reported by Ferreri et al[1] deserves further evaluation in a well-defined, more homogeneous patient population and with a predefined monitoring protocol for toxicity. Considering this regimen to be the standard for routine patient care and in the design of future studies seems premature.

*Agnieszka Korfel*
Charite University Medicine Berlin, Berlin, Germany

*Marc Chamberlain*
University of Washington, Seattle, WA

*Ed Neuwelt*
Oregon Health and Science University, Portland, OR

*Eckhard Thiel*
Charite University Medicine Berlin, Berlin, Germany

*Nancy Doolittle*
Oregon Health and Science University, Portland, OR

*Uwe Schlegel*
Ruhr-Universität Bochum, Bochum, Germany


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*Martin Dreyling*
University Hospital München, Großhadern, Germany

*James Rubenstein*
University of California, San Francisco, San Francisco, CA

*Lars Fischer*
Charite University Medicine Berlin, Berlin, Germany

*Magnus Björkholm*
Karolinska University Hospital Stockholm, Sweden

*Peter Martus*
University Tuebingen, Tuebingen, Germany

*Michael Weller*
University Hospital Zürich, Zürich, Switzerland

*Michael Glantz*
Penn State College of Medicine, Hershey, PA

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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**Agnieszka Korfel**
**Honoraria:** Mundipharma, RIEMSER, Piqur, Alexion Pharmaceuticals
**Consulting or Advisory Role:** Mundipharma, RIEMSER
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**Marc Chamberlain**
No relationship to disclose

**Ed Neuwelt**
No relationship to disclose

**Eckhard Thiel**
No relationship to disclose

**Nancy Doolittle**
No relationship to disclose

**Uwe Schlegel**
**Honoraria:** Roche
**Consulting or Advisory Role:** Roche
**Travel, Accommodations, Expenses:** Roche

**Martin Dreyling**
No relationship to disclose

**James Rubenstein**
**Research Funding:** Celgene, Genentech

**Lars Fischer**
No relationship to disclose

**Magnus Björkholm**
**Honoraria:** Roche
**Consulting or Advisory Role:** Shire, Celgene, MSD, Novartis, Tolero Pharmaceuticals

**Peter Martus**
No relationship to disclose

**Michael Weller**
**Honoraria:** Celldex, Merck, MSD, Roche, Novocure
**Consulting or Advisory Role:** ImmunoCellular Therapeutics, Magforce, Isarna, Pfizer, Tewa
**Research Funding:** Acceleron Pharma (Inst), Actelion (Inst), Roche (Inst), Isarna (Inst), Piqur (Inst), Bayer (Inst), MSD (Inst)

**Michael Glantz**
**Consulting or Advisory Role:** Abbvie
**Research Funding:** ImmunoCellular Therapeutics, Sunovian
**Travel, Accommodations, Expenses:** Abbvie


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